Combined Aspirin–Oral Anticoagulant Therapy Compared With Oral Anticoagulant Therapy Alone Among Patients at Risk for Cardiovascular Disease

A Meta-analysis of Randomized Trials

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Background: For patients receiving oral anticoagulant (OAC) therapy, deciding whether to add aspirin to their treatment is a common clinical scenario with no clear guidelines to aid practice. We performed a systematic review and meta-analysis of randomized controlled trials comparing these 2 treatment strategies (combined aspirin-OAC therapy vs OAC therapy alone) to assess the therapeutic benefits and risks.

Data Sources: Randomized controlled trials published up to June 2005 in MEDLINE, EMBASE, and Cochrane Library databases.

Study Selection: Randomized controlled trials with at least 3 months of follow-up that compared aspirin-OAC therapy with OAC therapy alone, in which OAC was administered to achieve the same target international normalized ratio or was given at the same fixed dose in both treatment arms.

Data Extraction: Two reviewers independently extracted data on study characteristics and outcomes. Pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated for study outcomes in patients receiving aspirin-OAC therapy and OAC therapy alone.

Data Synthesis: Ten studies were included, totaling 4180 patients. The risk for arterial thromboembolism was lower in patients receiving combined aspirin-OAC therapy compared with OAC therapy alone (OR, 0.66; 95% CI, 0.52-0.84). However, these benefits were limited to patients with a mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49). There was no difference in the risk for arterial thromboembolism with these treatments in patients with atrial fibrillation (OR, 0.99; 95% CI, 0.47-2.07) or coronary artery disease (OR, 0.69; 95% CI, 0.35-1.36). There was no difference in all-cause mortality with either treatment (OR, 0.98; 95% CI, 0.77-1.25). The risk for major bleeding was higher in patients receiving aspirin-OAC therapy compared with OAC therapy alone (OR, 1.43; 95% CI, 1.00-2.02).

Conclusion: Our findings question the current practice of using combined aspirin-OAC therapy except in patients with a mechanical heart valve, given the questionable benefits in reducing thromboembolic events and the increased risk of major bleeding.

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bleeding) of this treatment approach. Furthermore, aspirin therapy is an established risk factor for bleeding in patients who are receiving an OAC, and patients who receive combined aspirin-OAC therapy may be receiving a potentially harmful treatment without evidence for better efficacy compared with OAC therapy alone. Against this background, we performed a systematic review and meta-analysis of randomized trials comparing combined aspirin-OAC therapy with OAC therapy alone. Our objective was to determine if, for selected patients receiving OAC therapy, the current practice of adding aspirin to their treatment was supported by evidence that assessed the efficacy (arterial thromboembolism) and safety (major bleeding) of this treatment approach.

**METHODS**

**DATA SOURCES**

**Study Selection**

We searched the MEDLINE (1966 to June 2003), EMBASE (1980 to June 2003) and Cochrane Central Register of Controlled Trials (2005, issue 2) databases. The search strategy was supplemented by manually reviewing reference lists and by contacting content experts. Included studies assessed a broad spectrum of patients, irrespective of the clinical indication for antithrombotic therapy because the outcomes of interest are applicable to all patients who are receiving antithrombotic therapy.

Included studies satisfied the following 4 criteria: (1) randomized controlled trial in adult patients requiring OAC therapy; (2) compared combined aspirin-OAC therapy with OAC therapy alone, in which OAC therapy was administered to achieve the same target INR or was given with the same fixed dose in both treatment arms; (3) patients were followed up for 3 months or longer; and (4) at least 1 prespecified outcome (arterial thromboembolism, mortality, or major bleeding) was objectively documented. In studies with multiple publications, data were extracted from the most recent publication and, if required, earlier publications were used only to provide missing data.

**Study Quality Assessment**

Two reviewers (F.D. and W.L.), masked to the study authors and journals in which the studies were published, independently extracted data for arterial thromboembolism, all-cause mortality, and major bleeding. Arterial thromboembolism was defined as myocardial infarction, unstable angina requiring hospitalization, stroke, transient ischemic attack, or systemic embolism. All-cause mortality was defined as death from any cause. Major bleeding was defined as bleeding that required transfusion of 2 or more units of packed red blood cells, involved a critical site (eg, intracranial), or was fatal. If outcome data could not be extracted, the study authors were contacted by e-mail, with a reminder after 15 days. Disagreements regarding data extraction were resolved by consensus and discussion with a third reviewer (J.D.D.).

**STATISTICAL ANALYSES**

The $\kappa$ statistic was used to assess agreement between reviewers for study selection and quality. Pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method for arterial thromboembolism (with a separate analysis for fatal thromboembolism), all-cause mortality, and major bleeding (with separate analyses for intracranial and fatal bleeding) outcomes in patients receiving aspirin-OAC therapy and OAC therapy alone, using Review Manager statistical software (RevMan version 4.2.7; The Cochrane Collaboration, Oxford, England; 2004). The appropriateness of pooling the results from individual studies was assessed using the $I^2$ test for heterogeneity. The $I^2$ value describes the percentage of total variation across studies due to heterogeneity rather than chance. All analyses were initially done using a fixed-effects model, and if heterogeneity across studies was observed, the analyses were repeated using a random-effects model, which includes a measure of variance in the cal-

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Figure 1. Study selection process. INR indicates international normalized ratio; OAC, oral anticoagulant.
culation of pooled results.\textsuperscript{10} A sensitivity analysis was done in high-quality studies to assess the robustness of findings from the primary analyses. Publication bias was assessed using a funnel plot of effect size against standard error.\textsuperscript{17}

Subgroup analyses were done to assess the efficacy and safety of aspirin-OAC therapy and OAC therapy alone according to the clinical indication for OAC therapy (atrial fibrillation, mechanical heart valve, and CAD).

### RESULTS

#### DATA SOURCES

#### Study Selection

As shown in Figure 1, 858 potentially eligible studies were identified, of which 830 were excluded after reviewing the study abstracts, leaving 28 studies for a more detailed evaluation.\textsuperscript{18-45} Three additional studies were identified through a manual review of study bibliographies.\textsuperscript{46-48} Communication with 5 content experts did not identify any additional eligible studies. Of these 31, 21 were excluded for the following reasons: duplicate data in 12 studies\textsuperscript{*}; different intensities of OAC therapy were administered in the 2 treatment arms in 7 studies\textsuperscript{18-20,23,36,38,39}; OAC was compared with aspirin alone in 1 study\textsuperscript{40}; and the OAC group was not part of the original protocol but was added subsequently in 1 study.\textsuperscript{41} In total, 10 studies were therefore included in this meta-analysis.\textsuperscript{+} The interobserver agreement for study selection was excellent, with $\kappa = 0.99$.

#### Study Characteristics and Quality

The main characteristics of the included studies are given in Table 1. All included studies were published in English. A total of 4180 patients were studied, with study sample sizes ranging from 61 to 2545 patients. There were 5 studies of patients with mechanical heart valves,\textsuperscript{22,27,41,46,48} 2 studies of patients with atrial fibrillation,\textsuperscript{23,31} 2 studies of patients with CAD,\textsuperscript{24,42} and 1 study involving patients at high risk for cardiovascular disease.\textsuperscript{32} Low-dose aspirin ($\leq 100$ mg/d) was used in 6 studies\textsuperscript{22,24,25,32,41,42} and moderate to high-dose aspirin (200-1000 mg/d) in 4 studies.\textsuperscript{27,31,46,48} In 8 studies, the target INR was 1.8 or higher,\textsuperscript{22,24,25,27,31,32,41,42,46,48} while in the remainder it was 2.0 or higher.

As given in Table 2, 4 studies were rated as high quality;\textsuperscript{24,25,32,41} and 6 studies were rated as low quality.\textsuperscript{22,27,31,42,46,48} All studies had appropriate random allocation of treatment, 5 studies were double blind;\textsuperscript{24,25,32,41,46} 6 studies provided a description of patient withdrawals;\textsuperscript{24,25,27,32,41,42} and 3 studies had concealed treatment allocation.\textsuperscript{24,32,41}

### DATA SYNTHESIS

#### Primary Analyses

Data relating to the primary study outcomes (arterial thromboembolism, all-cause mortality, and major bleeding) and secondary study outcomes (fatal arterial thromboembolism, fatal major bleeding) are documented in Table 3.

#### Arterial Thromboembolism

Arterial thromboembolism occurred in 128 (6.3%) of 2023 patients who received aspirin-OAC therapy and 179 (8.8%) of 2036 patients who received OAC therapy alone. The risk for arterial thromboembolism was significantly lower with aspirin-OAC therapy than with OAC therapy (OR, 0.66; 95% CI, 0.52-0.84; absolute risk reduction, 2.5%; number needed to treat, 40). Ov-

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*References 21, 23, 26, 28, 30, 33-35, 37, 43, 45, and 47.

Major Bleeding. Major bleeding occurred in 80 (3.8%) of 2080 patients who received aspirin-OAC therapy and 60 (2.8%) of 2100 patients who received OAC therapy alone. The risk for major bleeding was significantly higher in patients receiving aspirin-OAC therapy alone, patients who received aspirin-OAC therapy had a lower risk for arterial thromboembolism (OR, 0.70; 95% CI, 0.52-0.93), and a documented trend toward increased major bleeding (OR, 1.38; 95% CI, 0.85-2.23). All-cause mortality did not appear to differ in the 2 treatment groups (OR, 0.97; 95% CI, 0.75-1.26).

Publication Bias. This was assessed with 3 funnel plots, which are available from the authors on request. These included 9 studies because 1 study did not provide data on thromboembolic events, studied no bleeding events, and 1 study had no deaths. The funnel plots for thromboembolic, mortality, and bleeding outcomes appeared symmetric, suggesting the absence of publication bias.

Secondary Analyses in Patient Subgroups

In patients with a mechanical heart valve, there was a significantly lower risk for arterial thromboembolism in patients who received aspirin-OAC therapy compared with OAC therapy alone (OR, 0.27; 95% CI, 0.15-0.49). There was no statistically significant difference in the risk for arterial thromboembolism with these treatments in patients with atrial fibrillation (OR, 0.99; 95% CI, 0.47-2.07) or CAD (OR, 0.69; 95% CI, 0.35-1.36). There was no difference in mortality between the 2 treatment groups in patients with atrial fibrillation (OR, 1.24; 95% CI, 0.50-3.04), in patients with a mechanical heart valve (OR, 0.66; 95% CI, 0.38-1.13), and in patients with CAD (OR, 0.86, 95% CI, 0.15-4.90). In patients with a mechanical heart valve, there was a significantly higher risk for major bleeding in patients who received aspirin-OAC therapy compared with OAC alone (OR, 1.49; 95% CI, 1.00-2.23). The risk for bleeding was not significantly different between treatments in patients with atrial fibrillation (OR, 1.02; 95% CI, 0.25-4.09). The data for bleeding outcomes in the 2 studies involving patients with CAD were not pooled because the OR for bleeding could not be calculated for only 1 of the studies in which no bleeding events were documented.

This study demonstrates that there is little support in the published literature for the common clinical practice of adding aspirin to OAC therapy except in selected patients with a mechanical heart valve.

The finding that aspirin-OAC therapy is associated with a lower risk for arterial thromboembolism compared with OAC therapy alone appears to be driven by the results of 3 trials in patients with a mechanical heart valve and 1 trial assessing the primary prevention of cardiovascular disease in high-risk patients. Data from the secondary analyses that compared combined aspirin-OAC therapy and OAC therapy alone according to the indication for anticoagulation showed a significantly lower risk for nonfatal arterial thromboembolism in patients with a mechanical heart valve but not in patients with atrial fibrillation or CAD. Furthermore, the primary analysis found no difference in mortality between aspirin-OAC therapy and OAC therapy alone, regardless of the patient level of risk.

Only 2 small randomized trials addressed the issue of combining aspirin and OAC therapy in patients with atrial fibrillation. These trials provided conflicting results: one trial (157 patients) found that, compared with OAC therapy alone, as-

<table>
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<th>Double-blind</th>
<th>Description of Withdrawals</th>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not specified; OAC, oral anticoagulant.
pirin-OAC therapy was associated with a nonsignificantly higher risk for arterial thromboembolism (OR, 3.29; 95% CI, 0.33-32.3)\textsuperscript{25}, the other trial (328 patients) found that aspirin-OAC therapy was associated with a nonsignificantly lower risk for arterial thromboembolism (OR, 0.82; 95% CI, 0.37-1.84).\textsuperscript{31} Only 1 trial was found to be of high quality,\textsuperscript{25} and neither study used the currently recommended therapeutic INR range between 2.0 and 3.0.

In contrast, 5 trials involving almost 1000 patients compared aspirin-OAC therapy with OAC therapy alone in patients with a mechanical prosthetic heart valve.\textsuperscript{22,27,41,46,48} In such patients, the use of aspirin-OAC therapy was associated with a significant reduction in the risk for arterial thromboembolism, although the risk for major bleeding appeared to be increased.

Our finding that aspirin-OAC therapy is associated with an increased risk for major bleeding is consistent with previous studies.\textsuperscript{2} Combined antithrombotic therapy, consisting of aspirin and OAC, aspirin and dipyridamole, or aspirin and clopidogrel, is known to increase the risk for bleeding compared with the use of a single antithrombotic agent.\textsuperscript{8,49,50} In a recent study that assessed 3566 patients with chronic atrial fibrillation who were receiving warfarin therapy targeted to achieve an INR of 2.0 to 3.0, patients who were receiving concomitant aspirin (\(\leq 100 \text{ mg/d} \)) had a more than 2-fold increased risk for major bleeding (OR, 2.41; 95% CI, 1.69-3.43).\textsuperscript{2}

There are potential weaknesses of our meta-analysis. The definition of arterial thromboembolism varied across studies. However, all events were clinically detected and associated with either direct morbidity and mortality (myocardial infarct and stroke) or the potential for increased future morbidity events (unstable angina and transient ischemic attack). In addition, the criteria for major bleeding varied across studies. We attempted to overcome this
### Table 1: Risk for Arterial Thromboembolism

<table>
<thead>
<tr>
<th>Source or Subcategory</th>
<th>OR, Fixed (95% CI)</th>
<th>Weight, %</th>
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<td>2/75</td>
<td>7.25</td>
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<td>Cohen et al.42 1990</td>
<td>16/37</td>
<td>4.22</td>
<td>1.07 (0.38-3.02)</td>
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<td>Meade et al.46 1992</td>
<td>71/1277</td>
<td>48.18</td>
<td>0.84 (0.61-1.17)</td>
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<tr>
<td>Turpie et al.31 1993</td>
<td>3/186</td>
<td>12.12</td>
<td>0.13 (0.04-0.46)</td>
</tr>
<tr>
<td>Gullov et al.31 1999</td>
<td>12/171</td>
<td>8.07</td>
<td>0.82 (0.37-1.84)</td>
</tr>
<tr>
<td>Laffort et al.27 2000</td>
<td>7/109</td>
<td>4.37</td>
<td>0.96 (0.34-2.74)</td>
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<tr>
<td>Huynh et al.24 2001</td>
<td>11/44</td>
<td>8.18</td>
<td>0.50 (0.20-1.24)</td>
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<tr>
<td>Lechat et al.24 2001</td>
<td>3/76</td>
<td>0.57</td>
<td>3.29 (0.33-32.31)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<td>2032</td>
<td>100.00 (0.62-0.84)</td>
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</table>

Total Events: 128 (OAC + Aspirin); 179 (OAC)
Test for Heterogeneity: \( \chi^2 = 18.97 \) (\( P = .02 \)); \( I^2 = 57.8\% \)
Test for Overall Effect: \( Z = 3.36 \) (\( P < .001 \))

### Table 2: Risk for All-Cause Mortality

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<th>Source or Subcategory</th>
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<th>Weight, %</th>
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<td>1/57</td>
<td>1.39</td>
<td>0.56 (0.05-6.37)</td>
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<tr>
<td>Dale et al.46 1980</td>
<td>3/75</td>
<td>4.42</td>
<td>0.47 (0.11-1.94)</td>
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<tr>
<td>Cohen et al.42 1990</td>
<td>0/37</td>
<td>1.35</td>
<td>0.21 (0.01-5.34)</td>
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<td>15.95</td>
<td>0.37 (0.17-0.84)</td>
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<td>4.38</td>
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<td>0.72</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<td>2089</td>
<td>100.00 (0.77-1.25)</td>
</tr>
</tbody>
</table>

Total Events: 139 (OAC + Aspirin); 141 (OAC)
Test for Heterogeneity: \( \chi^2 = 11.09 \) (\( P = .20 \)); \( I^2 = 27.8\% \)
Test for Overall Effect: \( Z = 0.15 \) (\( P = .88 \))

### Table 3: Risk for Major Bleeding

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<th>Source or Subcategory</th>
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<td>8.68</td>
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<td>2.10 (0.18-23.98)</td>
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<td>1.76</td>
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<td>3/57</td>
<td>8.43</td>
<td>0.66 (0.15-2.87)</td>
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<td><strong>Total (95% CI)</strong></td>
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<td>2089</td>
<td>100.00 (1.00-2.02)</td>
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</table>

Total Events: 80 (OAC + Aspirin); 60 (OAC)
Test for Heterogeneity: \( \chi^2 = 5.79 \) (\( P = .07 \)); \( I^2 = 0\% \)
Test for Overall Effect: \( Z = 1.98 \) (\( P = .05 \))

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**Figure 2.** Risk for arterial thromboembolism in patients receiving aspirin + oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.

**Figure 3.** Risk for all-cause mortality in patients receiving aspirin + oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.

**Figure 4.** Risk for major bleeding in patients receiving aspirin + oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.
by using a definition of major bleeding that would encompass the criteria used in various trials.11

The strengths of our meta-analysis include our use of a sensitivity analysis to assess the robustness of our findings in only high-quality studies, assessing for across-study heterogeneity for outcomes and, if necessary, accounting for this heterogeneity and assessing for publication bias. Our meta-analysis has advantages over other studies that compared aspirin-OAC and OAC therapy. Three prior meta-analyses assessed only patients with a mechanical heart valve51,52 or CAD53 and may have been underpowered to detect treatment effects, whereas we combined such patients. A fourth meta-analysis included studies in which the intensity of OAC therapy differed across treatment arms,13 which may not permit a valid assessment of the additive effects of aspirin to OAC therapy. We only included studies in which patients in both treatment arms received the same OAC treatment regimen.

Our findings question the current practice of using combined aspirin-OAC therapy in patients with atrial fibrillation and concomitant CAD or in patients at high risk for stroke. This issue is likely to affect a large number of patients, since approximately 2.5 million people in North America have chronic atrial fibrillation, of whom 30% to 40% have concomitant CAD and 10% to 15% are considered at high risk for stroke.3 Evidence for combined therapy in patients with a mechanical prosthetic heart valve is more compelling. In these patients, combination therapy is highly effective in reducing thromboembolic events.

In summary, our results suggest that, for patients receiving OAC therapy, the current practice of adding aspirin to their treatment should be considered carefully. The benefits in reducing thromboembolic events should be weighed against the increased risk of major bleeding. Large randomized trials are needed to assess the benefits and risks of these 2 treatment approaches in patients with both atrial fibrillation and CAD and high-risk patients with atrial fibrillation.

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Author Contributions: Study concept and design: Dentali and Douketis. Acquisition of data: Dentali, Lim, and Crowther. Analysis and interpretation of data: Dentali, Douketis, Lim, and Crowther. Drafting of the manuscript: Dentali, Douketis, and Crowther. Critical revision of the manuscript for important intellectual content: Dentali, Douketis, Lim, and Crowther.

Statistical analysis: Dentali and Lim. Obtained funding: Douketis and Crowther. Administrative, technical, and material support: Crowther. Study supervision: Douketis and Crowther.

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REFERENCES


